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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/694,758	CHAKRAVARTI, SHUKTI	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/27/07 has been entered.

Claim Status

2. Claims 1-41 have been canceled as filed 11/15/05.

Claims 42-52 are currently pending and are being examined in this application.

Election/Restrictions

3. Applicants elected Group IV (original Claims 5-7), and MMP-12 for the species of a gene, as acknowledged in the previous Office action mailed 7/30/02, p. 2. The pending claims 42-52) read on the originally elected Group of invention as previously acknowledged, and thus are examined in this application.

Priority

4. This application claims priority to U.S. Provisional Patent Application No. 60/160,835, filed 10/21/1999.

Specification

Sequence Rule Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reason(s) below:

Applicants' submission of a new "Sequence Listing" is not in compliance with Sequence Rule. Applicants are respectively directed to the attached "Notice to Comply" and the "Raw Sequence Listing Error Report" for additional information.

Applicants are respectively reminded that in order to be fully responsive to the instant Office action, a full compliance to the "Sequence Rule" is required.

Claim Rejections Withdrawn

6. In light of applicants' amendment to the claims, the following rejection is withdrawn:

A.) Claims 42-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by applicant's amendments to the claims.

However, new rejection under 35 U.S.C. 112, second paragraph is formulated below. See the claim rejection under 35 U.S.C. 112, second paragraph below.

B.) Upon further consideration, the following rejection is withdrawn: Claims 42-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroeterology, vol 114, No. 4, April 1998; previously cited) and in view of the instant specification disclosure.

Maintained Claim Rejections

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

8. Claims 42-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained over the newly added claims (42-52), and is also necessitated by applicant's amendments to the claims.

The instant claims recite a method for determining whether a test cell from a given tissue has an inflammatory bowel disease (IBD) or pre-IBD phenotype of a test cell from a given tissue, said method comprising:

(a) determining an expression level of a macrophage inflammatory protein-2/3 (GRO3) gene product, neutrophil lipocalin (HNL) gene product, macrophage elastase (MMP-12) gene product, elastase specific inhibitor (elafin) gene product, and type VI collagen α3 chain (COL6A3) gene product in said test cell;

(b) comparing the expression level of each of said gene products in said test cell to an expression level of the same gene product in a control cell of the given tissue type; and

(c) associating a difference in the expression level of at least one pf said gene products in said test cell from the expression level of the same gene product in said control cell with an IBD or pre-IBD phenotype in said test cell.

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to the decision of The Court of Appeals for the Federal Circuit, which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

The instant claims are drawn to a genus of methods for determining the gene expression level of a gene product in a sample. The instant claims are drawn to five genes (i.e. GRO3, HNL, elafin, COL6A3, and MMP-12). The instant claims are also drawn to compare the expression levels of the said genes, and "associating" the different levels with "IBD" or "pre-IBD" phenotypes.

The instant specification does not provide support for the entire claimed genus of methods of determining IBD or pre-IBD in a given tissue using the listed five genes. First, the instant specification does not provide common structure, or representative number of species for the claimed "IBD phenotype", or "pre-IBD phenotype". The instant specification also does not provide support for associating any difference in expression level of any of the five genes to any of the claimed IBD or pre-IBD phenotype.

Furthermore, the instant specification does not provide support for "associating a difference in the expression level" of at least the GRO3, HNL, and COL6A3 to a CD (Crohn's disease) phenotype or pre-CD phenotype. In Table 1 of the instant specification, the expression pattern for the said genes appear to be not different for cells from CD tissues. In addition, Applicants have not shown that the expression levels of various genes, and their association with the IBDs are representative of the entire claimed genus of "associating a difference in the expression level ... with an IBD or pre-IBD phenotype".

Thus, applicants are not in possession of the entire claimed genus of methods of determining for IBD or pre-IBD.

Furthermore, the instant claims and specification only define the specific genes by their GenBank accession numbers. The specific sequences for the probes that can hybridize to these genes are not provided. In addition, the GENBANK accession number do not provide a reference to a stable, know and non-changing source of information. GENBANK information may be updated and revised anytime (see http://www.ncbi.nih.gov/Genbank/index.html (2006) under the heading Updating or Revising a Sequence; cited previously), therefore, the sequence for the claimed genes could change anytime. A person of ordinary skill in the art would not be

able to envision that the applicants had possession of the recited invention as described. It is unclear as to what portion of the gene sequences are used, or suitable for the said probes for the array.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the instant specification has demonstrate the possession of the entire genus "IBD". (Reply, pp. 13-14).

Applicant's argument for defining IBD as to comprise two major subtypes, CD and UC, is partially persuasive. However, the instant claims are drawn to the entire genus of "IBD phenotype" or "pre-IBD phenotype". As pointed out by applications, CD and UC are the only two "major subtypes" of IBD. Applicants have not demonstrated the possession of the entire genus of IBD phenotypes of any cell from any tissue, or pre-IBD phenotypes of any cell from any tissue, as discussed in the rejection above.

Applicants argue the amendment to the instant specification to recite the specific nucleic acid sequences corresponding to each gene name would overcome the written description rejection. (Reply, p. 15)

However, applicant's proposed amendment to the specification (Sequence listing) is not entered due to sequence compliance issues, as discussed above.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Alexander and Poulakkainen

12. Claims 42-48, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp. 660-669; previously cited), and Poulakkainen (G4358; previously cited). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 10/23/06. The previous rejection over Claim 49 is withdrawn due applicant's amendment to the claims.

Alexander et al, throughout the publication, disclose a method to determine altered expression of protooncogenes (cell cycle related genes) in patients with inflammatory bowel disease (IBD), which reads on the determining gene expression of **clm 42**. The reference assayed transcripts of 15 protooncogenes (refer to IBD genes) in colonic epithelial cells of IBD patients and controls (e.g., see abstract). The reference discloses that increased levels (refers to the differential expression of the instant claim) of soluble mediators (e.g. Leukotrienes,

prostaglandins) of inflammation as well as the cells of immune system have been found to be present in the intestinal mucosa and submucosa of IBD patients (e.g., see page 660, last paragraph bridging first paragraph in page 661). The reference discloses expression of transcripts of eight growth factor receptor related genes in colonic epithelial cells of IBD patients and controls (i.e., see left column in page 661). These read on the comparison step of **clm 42**.

The reference discloses that the level of expression of *c-fos* in the involved IBD samples was about two fold higher than in the uninvolved IBD samples, which reads on the at least a factor of two difference in expression level of **clm 46**. The reference also teaches cells obtained from patients with UC and CD (Abstract of the reference), which reads on the IBDs of **clms 43 and 44**. The reference also teaches that certain genes expression levels are different in UC when compared to CD patients (Abstract of the reference), which reads on the distinguishing between UC and CD step of **clm 45**.

The reference also teaches samples are obtained from surgery (p. 661, right col., para 2), which reads on the sample of **clm 47**. The reference also teaches hybridization analysis (e.g. northern blotting) to analyze gene expression (p. 662, right col.), which reads on the method step of **clm 48**. The northern blotting membrane also reads on an array having a substrate (**clms 49-52**), because the northern blotting membrane has probes bound thereto and the probes are arranged in a two dimensional matrix format (see Figure 2 of the reference).

Overall, Alexander et al teach a method to determine the differential expression of genes involved in IBD.

Alexander et al do not specifically teach the five listed genes in the instant **clm 42**. However, the genes in listed in the instant Claim 42 (and Table 1 of the instant specification) are

not novel genes, and are well known for their role in IBD. The specification in page 19, discloses 'Table 1 indicates those sequences which are over- or underexpressed in a CD- or UC_derived cells relative to normal tissue.' Applicants in the specification disclose the GenBank accession numbers of the genes used in the claimed method. Thus, all the genes used in the claimed method are well known in the art.

Puolakkainen et al (G4358), throughout the publication, teach distinct expression profiles of stromelysin-s, collagenase and MMP-12 in intestinal ulcerations. As taught by Alexander et al, Crohn's disease (CD), and ulcerative colitis (UC) are part of larger group of IBDs (p. 660 of Alexander).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use all the known genes involved in IBD and use the genes (or probes) in array format to determine the IBD or pre-IBD phenotype.

A person of ordinary skill in the art would have been motivated to use all the known genes or genetic markers involved in IBD in an array format to screen IBD cells, such that the efficiency of the method improves (i.e., more markers used the more different mechanisms involved in IBD are determined). Because Alexander et al teach that the genes that are differentially expressed in IBD patients can be used as markers for development of colon cancer in IBD (Abstract, last lines), a person of ordinary skill in the art would have been motivated at the time of the invention was made to use the differentially expressed MMP-12 (as taught by Puolakkainen et al) as a gene marker for determining IBD phenotype of cells.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because the techniques for monitoring gene expression such as using DNA microarray and the specific genes (such as MMP-12) are known in the prior art such as taught by Alexander et al and Puolakkainen et al, who have demonstrated the detection of expression of various genes in IBD cells.

Discussion and Answer to Argument

13. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue that each of the cited references individually does not teach all element of the claimed invention (Reply, pp. 19+).

However, the above rejection is made over the combination of the cited references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Dieckgraefe and Poulakkainen

14. Claims 42-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dieckgraefe et al (Gastroeterology, vol 114, No. 4, April 1998; cited previously) and Poulakkainen (G4358;

cited previously). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 10/23/06.

Dieckgraefe et al, throughout the publication, disclose a method for identifying gene expressed in IBD, which reads on the determining gene expression of **clm 42**. The reference has used GeneChip expression monitoring system to examine mucosal gene expression in ulcerative colitis, Crohns' disease, and both in inflamed and non-inflamed non IBD specimens (Background section of the reference), which reads on the UC and DC of **clms 43 and 44**. The reference also teaches RNA isolated from the mucosa of colonic resection specimens was used to generate hybridization probes (See Methods), which reads on the surgical resection sample of **clm 47**. The reference also teaches light directed solid-phase combinatorial chemistry was used to generate oligonucleotide probe array (see Methods), which reads on the nucleic acid probes, array, and substrates of **clms 48-52**. The reference in the results section discloses that dramatic changes were seen in the expression of wide range of genes, genes were identified which appear to be specific markers for the specific diagnosis, disease activity and specific feature of histology, and specific genotype diagnosis for UC group, which read on the step of distinguishing between UC and CD of **clm 45**. The reference also teaches dramatic changes of gene expression for a wide range of genes (Results section of the reference), which reads on the at least a factor of two difference in expression of **clm 46**.

Dieckgraefe et al also teach the need to identify gene markers differentially expressed in CD and UC, and the need to use different genes that are differentially expressed to identify genotypes for the different diseases (such as CD and UC) for potential pharmaceutical purposes

(see Aims section of the reference). The reference further teaches host defense molecules are over expressed in IBD cells (Results section).

Dieckgraefe et al do not explicitly teach using MMP-12 as a gene marker for IBD determination.

However, the genes shown in Table 1 (which comprises MMP-12) of the instant specification are publicly known and available. Furthermore, **Puolakkainen** et al, throughout the publication, teach distinct expression profiles of stromelysin-s, collagenase and MMP-12 in intestinal ulcerations.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention to use all the known genes involved in IBD and use the genes (or probes) in array format to determine the IBD or pre-IBD phenotype.

A person of ordinary skill in the art would have been motivated to use all the known genes or genetic markers involved in IBD in an array format to screen IBD cells, such that the efficiency of the method improves (i.e., more markers used the more different mechanisms involved in IBD are determined). Because Dieckgraefe et al teach the need to identify gene markers differentially expressed in different diseases such as UC and CD for potential pharmaceutical purposes, and many host defense molecules are over expressed in IBD cells, a person of ordinary skill in the art would have been motivated at the time of the invention was made to use the differentially expressed MMP-12 (as taught by Puolakkainen et al) as a gene marker for determining IBD phenotype of cells.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because the techniques for monitoring gene expression such as

using DNA microarray and the specific genes (such as MMP-12) are known in the prior art such as taught by Dieckgraefe et al and Puolakkainen et al, who have demonstrated the detection of expression of various genes in IBD cells.

Discussion and Answer to Argument

15. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue that each of the cited references individually does not teach all element of the claimed invention (Reply, pp. 19+).

However, the above rejection is made over the combination of the cited references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

New Claim Rejections

Claim Rejections - 35 USC § 112

Second paragraph of 35 U.S.C. 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 42-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 recites the limitation "the given tissue type" in part (b). There is insufficient antecedent basis for this limitation in the claim.

Claim 42 recites the term "pre-IBD phenotype", which is indefinite. The instant specification does not specifically define the said term. It is not clear what phenotypic range is included for the so-called "pre-IBD phenotype" for a "test cell". The term "pre" is defined by the dictionary as "before" (Definition for "pre" from Cambridge Dictionary Online; Downloaded from ://dictionary.cambridge.org/define.asp?key=62175&dict=CALD on 5/29/07). Thus, the term can be broadly interpreted mean any phenotype before "IBD" phenotype. It is not clear to which range of stage of phenotype the term is referring.

Claim 42 appears to recite alternative limitations in step (or part) (a) of the claim. However, the listed gene products are not clearly recited in alternative format. It is not clear the "expression level" is the combination of expression level profiles from all the recited genes in step (a), or if the expression level is each one of the gene product. Applicants are respectively directed to MPEP 2173.05 (h) for guidance in alternative limitations.

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter Rejection

19. Claims 42-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 42 has been amendment as filed on 3/27/07. Claim 42 as amended recite step (a0 determining an expression level of a macrophage inflammatory protein-2β .... and type VI collagen α3 chain", which seem to recite an expression level based on the specific combination of the listed five genes. However, the instant specification does not provide support for the "combination" of genes.

If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claim 42 and its dependent claims represent new matter.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(Note: the instant claim numbers are in bold font.)

21. Claims 42-44, 46-48, and 50-52 are rejected under **35 U.S.C. 102(e)** as being anticipated by Cocks et al (US 6,607,879; 08/19/2003; Filed on 2/9/1998).

The instant claims recite a method for determining whether a test cell from a given tissue has an inflammatory bowel disease (IBD) or pre-IBD phenotype of a test cell from a given tissue, said method comprising:

(a) determining an expression level of a macrophage inflammatory protein-2/3 (GRO3) gene product, neutrophil lipocalin (HNL) gene product, macrophage elastase (MMP-12) gene product, elastase specific inhibitor (elafin) gene product, and type VI collagen α3 chain (COL6A3) gene product in said test cell;

(b) comparing the expression level of each of said gene products in said test cell to an expression level of the same gene product in a control cell of the given tissue type; and

(c) associating a difference in the expression level of at least one pf said gene products in said test cell from the expression level of the same gene product in said control cell with an IBD or pre-IBD phenotype in said test cell.

Cocks et al, throughout the patent, teach methods of diagnosing or monitoring diseases such as Crohn's diseases, and ulcerative colitis (IBDs) using DNA microarray (Abstract and Claims 4-5 of the reference), which reads on the IBDs of **clm 42-44**, and the array method of **clm 48**. The reference also teaches that SEQ ID No 1100 is human cytokine (GRO-γ) (See Table 1 of the reference), which reads on GRO3 of **clm 42**.

The reference further teaches that the transcripts (mRNA) used with the array are obtained from various sources such as inflamed samples and noninflamed biological samples from various tissues such as hematopoietic tissues or colon tissues (Col. 7, 1st paragraph and lines 10-25), which would read on gene product from a test cell and a control cell (step b) of **clm 42**, and the tissue sample of **clm 47**. In addition, the reference teaches comparing the hybridization pattern from diseased and non-diseased samples (Claim 4), which reads on steps (b)-(c) of **clm 42**.

The reference teaches cDNAs of various genes are immobilized on a substrate and are hybridizable elements on a microarray (Claims 2 and 3 of the reference), which reads on nucleic acid probes that specifically hybridize to the gene product of **clm 49**. The reference further teaches that transcript levels are preferably at least about 2xhigher in a diseased sample than in the nondiseased sample (Col. 7, lines 22-25), which reads on the expression level of **clm 46**. Furthermore, the reference teaches that the polynucleotide probes can be synthesized on the surface of the substrate by using covalent bonding to the substrate (Col. 10, lines 20-22, for example), and the substrates used could be chips, membrane, plates, etc. (Col. 10, lines 1-5), which read on the array and its substrate of **clms 49-52**.

Claim Rejections - 35 USC § 103

Alexander and others

22. Claims 42-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp. 660-669; previously cited), in view of Poulakkainen (G4358; previously cited) and Dieckgraefe et al (Gastroeterology, vol 114, No. 4, April 1998; cited previously). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 10/23/06.

The combination of Alexander and Poulakkainen references teaches using various gene expression in cells from patients with IBD, as discussed above.

The combination of said references does not expressly teach using probes with length of 12-40 nucleotides as recited **clm 49**.

Dieckgraefe et al (G4358), throughout the publication, teach using probes with length of 25 nucleotides.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use probes with specific length to detect gene expression product.

A person of ordinary skill in the art would have been motivated to use probes with specific length to detect gene expression, because probes with different lengths are known in the art and they can be used to represent diverse genes, as taught by Dieckgraefe et al.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because the techniques for generating probes with certain length is known in the art, as evidenced by Dieckgraefe et al.

Cock and others

23. Claims 42-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cocks et al (US 6,607,879; 08/19/2003; Filed on 2/9/1998), in view of Alexander et al (Digestive Diseases and Sciences, Vol. 41, No. 4 (April 1996), pp. 660-669; previously cited) and Dieckgraefe et al (Gastroeterology, vol 114, No. 4, April 1998; cited previously).

Cocks et al, throughout the patent, teach methods of diagnosing or monitoring diseases such as Crohn's diseases, and ulcerative colitis (IBDs) using DNA microarray, as discussed above.

Cocks et al do not expressly teach distinguishing between UC and CD as recited in **lcm 45**. The reference also does not explicitly teach using probes with lengths ranging from 12-40 nucleotides, as recited in **clm 49**.

However, Dieckgraefe et al (G4358), throughout the publication, teach using probes with length of 25 nucleotides.

Alexander et al, teach that certain genes expression levels are different in UC when compared to CD patients (Abstract of the reference), which reads on the distinguishing between UC and CD step of **clm 45**.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use probes with specific length to detect gene expression product, and to use the expression profile to distinguish between UC and CD.

A person of ordinary skill in the art would have been motivated to use probes with specific length to detect gene expression, because probes with different lengths are known in the art and they can be used to represent diverse genes, as taught by Dieckgraefe et al.

A person of ordinary skill in the art would have been motivated to different gene expression to distinguish between UC and CD, because differential gene expression between UC and CD are known, as well as the need to distinguish between two types of diseases.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications because the techniques for generating probes with certain length is known in the art, as evidenced by Dieckgraefe et al, and the differential gene expression for different subtypes of IBD is known, as taught by Alexander.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SL/
Art Unit 1639
6/8/07

/Jon D. Epperson/

Primary Examiner, Art Unit 1639

Notice to Comply	Application No. 09694758	Applicant(s) CHAKRAVARTI, SHUKTI	
	Examiner Sue Liu	Art Unit 1639	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☒ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See attached "Error Report".

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
For CRF Submission Help, call (571) 272-2501/2583.
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

STIC Biotechnology Systems Branch

RAW SEQUENCE LISTING ERROR REPORT

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) detected errors when processing the following computer readable form:

Application Serial Number: 09/694,758
Source: IFW16
Date Processed by STIC: 3/29/07

THE ATTACHED PRINTOUT EXPLAINS DETECTED ERRORS.
PLEASE FORWARD THIS INFORMATION TO THE APPLICANT BY EITHER:
1) **INCLUDING A COPY OF THIS PRINTOUT IN YOUR NEXT COMMUNICATION TO THE APPLICANT, WITH A NOTICE TO COMPLY or,**
2) **TELEPHONING APPLICANT AND FAXING A COPY OF THIS PRINTOUT, WITH A NOTICE TO COMPLY**

FOR CRF SUBMISSION AND PATENTIN SOFTWARE QUESTIONS, PLEASE CONTACT MARK SPENCER, TELEPHONE: 571-272-2510; FAX: 571-273-0221

TO **REDUCE** ERRORED SEQUENCE LISTINGS, **PLEASE** USE THE **CHECKER VERSION 4.4.0 PROGRAM**, ACCESSIBLE THROUGH THE U.S. PATENT AND TRADEMARK OFFICE WEBSITE. SEE BELOW FOR ADDRESS:

http://www.uspto.gov/web/offices/pac/checker/chkrnote.htm

Applicants submitting genetic sequence information electronically on diskette or CD-Rom should be aware that there is a possibility that the disk/CD-Rom may have been affected by treatment given to all incoming mail.
Please consider using alternate methods of submission for the disk/CD-Rom or replacement disk/CD-Rom.
Any reply including a sequence listing in electronic form should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office, and instead should be sent via the following to the indicated addresses:

1. EFS-Bio (<**http://www.uspto.gov/ebc/efs/downloads/documents.htm**> , **EFS Submission User Manual** - ePAVE)
2. **U.S. Postal Service:** Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
3. **Hand Carry, Federal Express, United Parcel Service, or other delivery service (EFFECTIVE 01/14/05):** U.S. Patent and Trademark Office, Mail Stop Sequence, Customer Window, Randolph Building, 401 Dulany Street, Alexandria, VA 22314

Revised 01/10/06

IFW16

RAW SEQUENCE LISTING
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DATE: 03/29/2007
TIME: 10:28:38

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Case Western Reserve University

<120> TITLE OF INVENTION: Gene Expression Profiling of Inflammatory Bowel Disease

<130> FILE REFERENCE: 021825-004710US

<140> CURRENT APPLICATION NUMBER: US 09/694,758

(pg. 7)

<141> CURRENT FILING DATE: 2000-10-23

<150> PRIOR APPLICATION NUMBER: US 60/160,835

<151> PRIOR FILING DATE: 1999-10-21

<160> NUMBER OF SEQ ID NOS: 145

<170> SOFTWARE: PatentIn Ver. 2.1

Does Not Comply
Corrected Diskette Needed

(pg. 6)

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PATENT APPLICATION: US/09/694,758 TIME: 10:28:38

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205 ttattttagg gctgagaatt cataaaaaaa ttcattctct gtggtatcca agaatcagtg 3420
206 aagatgccag tgaaacttca agcaaatcta cttcaacact tcatgtattg tgtgggtctg 3480
207 ttgtagggtt gccagatgca atacaagatt cctggttaaa tttgaatttc agtaaacaat 3540
208 gaatagtttt tcattgtacc atgaaatatc cagaacatac ttatatgtaa agtattattt 3600
209 atttgaatct acaaaaaaca acaaataatt tttaaatata aggattttcc tagatattgc 3660
210 acgggagaat atacaaatag caaaattggg ccaagggcca agagaatatc cgaactttaa 3720
211 tttcaggaat tgaatgggtt tgctagaatg tgatatttga agcatcacat aaaaatgatg 3780
212 ggacaataaa ttttgccata aagtcaaatt tagctggaaa tcctggattt ttttctgtta 3840
213 aatctggcaa ccctagtctg ctagccagga tccacaagtc cttgttccac tgtgccttgg 3900

RAW SEQUENCE LISTING DATE: 03/29/2007
PATENT APPLICATION: US/09/694,758 TIME: 10:28:38

Input Set : A:\-47-1.APP
Output Set: N:\CRF4\03292007\I694758.raw

214 tttctccttt atttctaagt ggaaaaagta ttagccacca tcttacctca cagtgatgtt 3960
215 gtgaggacat gtggaagcac tttaagtttt ttcatcataa cataaattat tttcaagtgt 4020
216 aacttattaa cctatttatt atttatgtat ttatttaagc atcaaatatt tgtgcaagaa 4080
217 tttggaaaaa tagaagatga atcattgatt gaatagttat aaagatgtta tagtaaattt 4140
218 attttatttt agatattaaa tgatgtttta ttagataaat ttcaatcagg gtttttagat 4200
219 taaacaaaca aacaattggg tacccagtta aattttcatt tcagatatac aacaaataat 4260
220 tttttagtat aagtacatta ttgtttatct gaaattttaa ttgaactaac aatcctagtt 4320
221 tgatactccc agtcttgtca ttgccagctg tgttggtagt gctgtgttga attacggaat 4380
222 aatgagttag aactattaaa acagccaaaa ctccacagtc aatattagta atttcttgct 4440
223 ggttgaaact tgtttattat gtacaaatag attcttataa tattatttaa atgactgcat 4500
224 ttttaaatac aaggctttat atttttaact ttagtgtttt tatgtgctct ccaaattttt 4560
225 tttactgttt ctgattgtat ggaaatataa aagtaaatat gaaacattta aaatataatt 4620
226 tgttgtcaaa gtaatcaagt gtttgtcttt tttttagttt tagcttattg ggattctctt 4680
227 tgtttatatt taaaattata ctttgattta gaaaacataa atgcttcccc ttagcatttt 4740
228 gttatggaaa attacaaact tttatttttа gaaaacagaa ctcctttcca gaaataggtt 4800
229 acaaacagta gtgtcctcca cagaatgttg gaaatgtttt caactcccca ctgtatacta 4860
230 tcttgctaat aagtctgtct tcagatttcg attaaccggt ttgtatgtct gtgcacttta 4920
231 gcatagctgg acattaaaga ggaaagagag tacatattat aagttgctta tcagtaactg 4980
232 aggagtaaaa ctgataaatg tgaggcaaag aagtttaaaa tatggttaaa gcctaagcat 5040
233 atttgcaaac aaatcaaaca atactctgag aagtaaaaac ataattattt aattaacaaa 5100
234 tttcagtgga taaattttat aacaaattag acacagttga aaataaaatt agaaaactag 5160
235 aaaatagaac aaaagaaact tctggaattc a 5191
238 <210> SEQ ID NO: 5
239 <211> LENGTH: 905
240 <212> TYPE: DNA
241 <213> ORGANISM: Homo sapiens
243 <220> FEATURE:
244 <223> OTHER INFORMATION: interferon-induced transmembrane protein 2
245 (IFITM2); interferon inducible protein 1-8D
247 <400> SEQUENCE: 5
248 caacacaggg gcagtctcca ggacctccac accattaaca agatgagcct tgtgctccct 60
249 tgggctctag agaggaagcc cctctgagcc ctcagcccct ctttcctccc tctcctaaag 120
250 taatttgatc ctcaggaatt tgttctgccc tcatctggcc ctggccagct ctgcatttga 180
251 caaatgccag gaagaggaaa ctgttgagaa aacggaacta ctggggaaag ggagggctca 240
252 ctgagaacca tcccggtaac ccgaccgccg ctggtcacca tgaaccacat tgtgcaaacc 300
253 ttctctcctg tcaacagcgg ccagcctccc aactacgaga tgctcaagga ggagcaggaa 360
254 gtggctatgc tgggggggcc ccacaaccct gctcccccga cgtccaccgt gatccacatc 420
255 cgcagcgaga cctccgtgcc tgaccatgtc gtctggtccc tgttcaacac cctcttcatg 480
256 aacacctgct gcctgggctt catagcattc gcctactccg tgaagtctag ggacaggaag 540
257 atggttggcg acgtgaccgg ggcccaggcc tatgcctcca ccgccaagtg cctgaacatc 600
258 tgggccctga ttttgggcat cttcatgacc attctgctcg tcatcatccc agtgttggtc 660
259 gtccaggccc agcgatagat caggaggcat cattgaggcc aggagctctg cccgtgacct 720
260 gtatcccacg tactctatct tccattcctc gccctgcccc cagaggccag gagctctgcc 780
261 cttgacctgt attccactta ctccaccttc cattcctcgc cctgtcccca cagccgagtc 840
262 ctgcatcagc cctttatcct cacacgcttt tctacaatgg cattcaataa agtgtatatg 900
263 tttct 905
266 <210> SEQ ID NO: 6
267 <211> LENGTH: 696
268 <212> TYPE: DNA

<210> 9
<211> 9721
<212> DNA
<213> Homo sapiens

<220>
<223> prointerleukin 1 beta (pro-IL-1beta);
interleukin-1 beta precursor; catabolin

<400> 9
agaaagaaag agagagagaa agaaaagaaa gaggaaggaa ggaaggaagg aagaaagaca 60
ggctctgagg aaggtggcag ttcctacaac gggagaacca gtggttaatt tgcaaagtgg 120
atcctgtgga ggcannncaga ggagtcccct aggccaccca gacagggctt ttagctatct 180
gcaggccaga caccaaattt caggagggct cagtgttagg aatggattat ggcttatcaa 240
attcacagga aactaacatg ttgaacagct tttagatttc ctgtggaaaa tataacttac 300
taaagatgga gttcttgtga ctgactcctg atatcaagat actgggagcc aaattaaaaa 360
tcagaaggct gcttggagag caagtccatg aaatgctctt tttcccacag tagaacctat 420
ttccctcgtg tctcaaatac ttgcacagag gctcactccc ttggataatg cagagcgagc 480
acgatacctg gcacatacta atttgaataa aatgctgtca aattcccatt cacccattca 540
agcagcaaac tctatctcac ctgaatgtac atgccaggca ctgtgctaga cttggctcaa 600
aaagatttca gtttcctgga ggaaccagga gggcaaggtt tcaactcagt gctataagaa 660
gtgttacagg ctggacacgg tggctcacgc ctgtaatccc aacatttggg aggccgaggc 720
gggcagatca caaggtcagg agatcgagac catcctggct aacatggtga aaccctgtct 780
ctactaaaaa tacaaaaaat tagccgggcg ttggcggcag gtgcctgtag tcccagctgc 840
tggggaggct gaggcaggag aatggtgtga acccgggagg cggaacttgc agggggccga 900
gatcgtgcca ctgcactcca gcctgggcga cagagtgaga ctctgtctca aaaaaaaaaa 960
aaaagtgtta tgatgcagac ctgtcaaaga ggcaaaggag ggtgttccta cactccaggc 1020
actgttcata acctggactc tcattcattc tacaaatgga gggctcccct gggcagatcc 1080
ctggagcagg cactttgctg gtgtctcggt taaagagaaa ctgataactc ttggtattac 1140
caagagatag agtctcagat ggatattctt acagaaacaa tattcccact tttcagagtt 1200
caccaaaaaa tcattttagg cagagctcat ctggcattga tctggttcat ccatgagatt 1260
ggctagggta acagcacctg gtcttgcagg gttgtgtgag cttatctcca gggttgcccc 1320
aactccgtca ggagcctgaa ccctgcatac cgtatgttct ctgccccagc caagaaaggt 1380
caatttttctc ctcagaggct cctgcaattg acagagagct cccgaggcag agaacagcac 1440
ccaaggtaga gacccacacc ctcaatacag acagggaggg ctattggccc ttcattgtac 1500
ccatttatcc atctgtaagt gggaagattc ctaaacttaa gtacaaagaa gtgaatgaag 1560
aaaagtatgt gcatgtataa atctgtgtgt cttccacttt gtcccacata tactaaattt 1620
aaacattctt ctaacgtggg aaaatccagt attttaatgt ggacatcaac tgcacaacga 1680
ttgtcaggaa aacaatgcat atttgcatgg tgatacattt gcaaaatgtg tcatagtttg 1740
ctactccttg cccttccatg aaccagagaa ttatctcagt ttattagtcc cctcccctaa 1800
gaagcttcca ccaatactct tttccccttt cctttaactt gattgtgaaa tcaggtattc 1860
aacagagaaa tttctcagcc tcctacttct gcttttgaaa gctataaaaa cagcgaggga 1920
gaaactggca gataccaaac ctcttcgagg cacaaggcac aacaggctgc tctgggattc 1980
tcttcagcca atcttcattg ctcaagtatg actttaatct tccttacaac taggtgctaa 2040
gggagtctct ctgtctctct gcctctttgt gtgtatgcat attctctctc tctctctctt 2100
tctttctctg tctctcctct ccttcctctc tgcctcctct ctcagctttt tgcaaaaatg 2160
ccaggtgtaa tataatgctt atgactcggg aaatattctg ggaatggata ctgcttatct 2220
aacagctgac accctaaagg ttagtgtcaa agcctctgct ccagctctcc tagccaatac 2280
attgctagtt ggggtttggt ttagcaaatg cttttctcta gacccaaagg acttctcttt 2340
cacacattca ttcatttact cagagatcat ttctttgcat gactgccatg cactggatgc 2400
tgagagaaat cacacatgaa cgtagccgtc atggggaagt cactcatttt ctccttttta 2460
cacaggtgtc tgaagcagcc atggcagaag tacctgagct cgccagtgaa atgatggctt 2520
attacaggtc agtggagacg ctgagaccag taacatgagc aggtctcctc tttcaagagt 2580
agagtgttat ctgtgcttgg agaccagatt tttcccctaa attgcctctt tcagtggcaa 2640
acagggtgcc aagtaaatct gatttaaaga ctacttttccc attacaagtc cctccagcct 2700
tgggacctgg aggctatcca gatgtgttgt tgcaagggct tcctgcagag gcaaatgggg 2760
agaaaagatt ccaagcccac aatacaagga atcccctttgc aaagtgtggc ttggagggag 2820

pls explain "N" locations. See error explanation on page 8.

The type of errors shown exist throughout the Sequence Listing. Please check subsequent sequences for similar errors.

RAW SEQUENCE LISTING ERROR SUMMARY DATE: 03/29/2007
PATENT APPLICATION: US/09/694,758 TIME: 10:28:39

Input Set : A:\-47-1.APP
Output Set: N:\CRF4\03292007\I694758.raw

Please Note:
Use of n and/or Xaa have been detected in the Sequence Listing. Please review the Sequence Listing to ensure that a corresponding explanation is presented in the <220> to <223> fields of each sequence which presents at least one n or Xaa.

Seq#:9; N Pos. 135,136
Seq#:17; N Pos. 1240,1241,1242,1243,1244,1245,1246,1247,1248,1249,1250,1251
Seq#:17; N Pos. 1252,1253,1254,1255,1256,1257,1258,1259,1260,1261,1262,1263
Seq#:17; N Pos. 1264,1265,1266,1267,1268,1269,1270,1271,1272,1273,1274,1275
Seq#:17; N Pos. 1276,1277,1278,1279,1280,2111,2112,2113,2114,2115,2116,2117
Seq#:17; N Pos. 2118,2119,2120,2121,2122,2123,2124,2125,2126,2127,2128,2129
Seq#:17; N Pos. 2130,2131,2132,2133,2134,2135,2136,2822
Seq#:37; N Pos. 1415,1421,1422,1423,1424,1458
Seq#:38; N Pos. 689,739,744
Seq#:85; N Pos. 2255,2256
Seq#:86; N Pos. 27,46
Seq#:89; N Pos. 2509
Seq#:136; N Pos. 511

VARIABLE LOCATION SUMMARY DATE: 03/29/2007
PATENT APPLICATION: US/09/694,758 TIME: 10:28:39

Input Set : A:\-47-1.APP
Output Set: N:\CRF4\03292007\I694758.raw

Error Explanation: 2

Use of n's or Xaa's(NEW RULES):
Use of n's and/or Xaa's have been detected in the Sequence Listing.
Use of <220> to <223> is MANDATORY if n's or Xaa's are present.
in <220> to <223> section, please explain location of n or Xaa, and which residue n or Xaa represents.

Seq#:9; N Pos. 135,136
Seq#:17; N Pos. 1240,1241,1242,1243,1244,1245,1246,1247,1248,1249,1250,1251
Seq#:17; N Pos. 1252,1253,1254,1255,1256,1257,1258,1259,1260,1261,1262,1263
Seq#:17; N Pos. 1264,1265,1266,1267,1268,1269,1270,1271,1272,1273,1274,1275
Seq#:17; N Pos. 1276,1277,1278,1279,1280,2111,2112,2113,2114,2115,2116,2117
Seq#:17; N Pos. 2118,2119,2120,2121,2122,2123,2124,2125,2126,2127,2128,2129
Seq#:17; N Pos. 2130,2131,2132,2133,2134,2135,2136,2822
Seq#:37; N Pos. 1415,1421,1422,1423,1424,1458
Seq#:38; N Pos. 689,739,744
Seq#:85; N Pos. 2255,2256
Seq#:86; N Pos. 27,46
Seq#:89; N Pos. 2509
Seq#:136; N Pos. 511

VERIFICATION SUMMARY DATE: 03/29/2007
PATENT APPLICATION: US/09/694,758 TIME: 10:28:39

Input Set : A:\-47-1.APP
Output Set: N:\CRF4\03292007\I694758.raw

L:355 M:258 W: Mandatory Feature missing, <221> Tag not found for SEQ ID#:9
L:355 M:258 W: Mandatory Feature missing, <222> Tag not found for SEQ ID#:9
L:355 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:9 after pos.:120
L:868 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:17 after pos.:1200
M:341 Repeated in SeqNo=17
L:1833 M:258 W: Mandatory Feature missing, <221> Tag not found for SEQ ID#:37
L:1833 M:258 W: Mandatory Feature missing, <222> Tag not found for SEQ ID#:37
L:1833 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:37 after pos.:1380
M:341 Repeated in SeqNo=37
L:1866 M:258 W: Mandatory Feature missing, <221> Tag not found for SEQ ID#:38
L:1866 M:258 W: Mandatory Feature missing, <222> Tag not found for SEQ ID#:38
L:1866 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:38 after pos.:660
M:341 Repeated in SeqNo=38
L:4402 M:258 W: Mandatory Feature missing, <221> Tag not found for SEQ ID#:85
L:4402 M:258 W: Mandatory Feature missing, <222> Tag not found for SEQ ID#:85
L:4402 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:85 after pos.:2220
L:4417 M:258 W: Mandatory Feature missing, <221> Tag not found for SEQ ID#:86
L:4417 M:258 W: Mandatory Feature missing, <222> Tag not found for SEQ ID#:86
L:4417 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:86 after pos.:0
L:4800 M:258 W: Mandatory Feature missing, <221> Tag not found for SEQ ID#:89
L:4800 M:258 W: Mandatory Feature missing, <222> Tag not found for SEQ ID#:89
L:4800 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:89 after pos.:2460
L:7627 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:136 after pos.:480
L:7926 M:259 W: Allowed number of lines exceeded, <223> Other Information: